5 We Claim:

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- 1. A method for inferring a gene network, comprising
- (a) providing an inferential model of possible gene networks of an organism including defining a search space;
  - (b) selecting a biologically relevant subspace of said search space; and
- (c) calculating an optimal solution in said selected subspace by repeatedly applying an algorithm that computes small gene networks optimally.
- 2. The method of claim 1, wherein said inferential model is a Bayesian network estimation model.
  - 3. The method of claim 1, wherein said biologically relevant subspace includes genes relating to a metabolic pathway of said organism.
- 20 4. The method of claim 1, wherein said algorithm comprises the steps:
  - (a) compute  $F(g, \phi) = s(g, \phi)$  for all  $g \in G$ ;
  - (b) for all  $A\subseteq G$ ,  $A\neq \phi$  and all  $g\in G$  compute F(g,A) as  $\min\{s(g,A),\min_{\tilde{a}\in A}F(g,A-\{a\})\};$ 
    - (c) set  $M(\phi) = \phi$ ,
- 25 (d) for all  $A \subseteq G$ ,  $A \neq \phi$ , do the following steps:
  - (i) compute  $g^* = \arg\min_{g \in A} (F(g, A \{g\}) + Q^{A \{g\}})(M(A \{g\}))$ ; and
  - (ii) for all  $1 \le i < |A|$ , set  $M(A)(i) = M(A \{g^*\})(i)$ , and M(A)(|A|) = g

\*; and

- (e) return  $Q^G(M(G))$ .
- The method of claim 4, wherein said algorithm is modified according to the steps of:
  - (a) in the computation of F in Step 1 and Step 2, compute only F(g,A) for all  $g \in S_i$  and all  $A \subseteq C_g$ ; and

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5 (b). replace the term  $F(g, A - \{g\})$  in Step 4a by  $F(g, (C_g = S_i) \cup (C_g \cap A))$ .

6. The method of claim 1, wherein an optimal network N has a definition:  $score(N) = \sum_{g \in G} s(g, P^N(g))$ .

- 10 7. The method of claim 1, wherein said algorithm comprises the steps:
  - (a) cluster genes in G such that no cluster is larger than c genes;
  - (b) sort the clusters by decreasing size:  $C_1, \ldots, C_n$ ;
  - (c) for each  $i \in \{1, ..., n\}$  and for each  $g \in C_b$  select up to m candidate parents from  $C_1 \bigcup ... \bigcup C_n$ ; and
- 15 (d) compute an optimal gene network model using Theorem 1.2.
  - 8. The method of claim 1, wherein said algorithm comprises the steps:
  - (a) group genes in G in groups  $C_i$  with  $|C_i| \le c$  and sort them according to biological knowledge:  $C_1, \ldots, C_n$ ;
- 20 (b) for each  $i \in \{1, ..., n\}$  and for each gene  $g \in C_i$ , select up to m candidate parents from  $C_1 \cup ... \cup C_i$ ; and
  - (c) compute an optimal gene network model using Theorem 2.
  - 9. The method of claim 1, wherein said algorithm comprises the steps:
- 25 (a) compute  $F(g, \phi) = s(g, \phi)$  for all  $g \in G$ ;
  - (b) for all  $A \subseteq G$ ,  $A \ne \phi$  and all  $g \in G$  compute F(g, A) as  $\min\{s(g,A), \min_{\tilde{a} \in A} F(g,A-\{a\})\}$ ;
    - (cc) set  $M(\phi) = \phi$ ,
    - (d) for all  $A \subseteq G$ ,  $A \neq \phi$ , do the following two steps:
      - (i) compute  $g^* = \arg\min_{g \in A} (F(g, A \{g\}) + Q^{A \{g\}})(M(A \{g\})))$ ; and
      - (ii) For all  $1 \le i < |A|$ , set  $M(A)(i) = M(A \{g^*\})(i)$ , and M(A)(|A|) = g

\*; and

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- (e) return  $Q^G(M(G))$ .
- 10. The method of claim 1, wherein said algorithm comprises the steps:

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5 (a) set  $F^{m}(g, \phi, 1) = \phi$ ,  $S^{m}(g, \phi, 1) = s(g, \phi)$  for all  $g \in G$ ;

- (b) for all  $g \in G$ , all  $A \subseteq G$ ,  $A \ne N$  and all  $n \le m$  do the following two steps:
- (i) select  $B^* \subseteq A$  from  $\{B \subseteq A \mid B = A \lor B = F^m(g, A \{h\}, p), h \in A, p \le m\} \{F^m(g, A, p) \mid p \le n\}$  such that  $s(g, B^*)$  is minimized; and
  - (ii) set  $F^{m}(g,A,n)=B^{*}$ ,  $S^{m}(g,A,n)=s(g,B^{*})$ ;
- (c) set  $M^m(\phi,1) = \phi$  and  $D^m(\phi,1) = \phi$ ,

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 $N_i$ ;

- (d) for all  $A \subseteq G$ ,  $\phi$ , and all  $n \le m$  do the following three steps:
- (i) choose a triple  $(g,p,q) \in A$  x  $IN_{\leq m}$  x  $IN_{\leq m}$  such that  $score(Q^{A-\{g\}}(M^m(A-\{g\},p),D^m(A-\{g\},p)))+S^m(g,A-\{g\},q)$  is minimized and (g,p,q) induces a network different from  $Q^A(M^m(A,r),D^m(A,r))$  for r < n;
- 15 (ii)  $\operatorname{set} M^{m}(A,n)(i)=M^{m}(A-\{g\},p)(i) \text{ for } i<|A|, \text{ and } M^{m}(A,n)(|A|)=g;$  and
  - (iii) let v denote  $D^m(A-\{g\},p)$ . Set  $w \in IN^{|A|}$  as  $w_i=v_i$  for all I < |A| and |A| = q and set  $D^m(A,n) = w$ ; and
    - (e) return  $Q^G(M^m(G,i),D^m(G,i))$  for all  $i \le m$ .

11. The method of any of claims 1-10, wherein reliability of an enumerated gene network, comprising the steps:

- (a) enumerate the most likely gene network models  $N_i$ ,  $1 \le i \le n$ ;
- (b) for every  $g, h \in 0G$ , count the occurrences of the edge (g,h) in the networks
- (c) select all edges (g,h) with at least c occurrences;
- (d) for all subsets M of the set of selected edges with |M| = k, count the networks including all edges in MI; and
  - (e) return all motives M with at least c occurrences.

12. The method of any of claims 1-11, further comprising calculating a scoring function selected from the group consisting of BRNC score, BDe score and MDL score.

- 35 13. A method for determining a gene network as substantially described herein.
  - 14. A storage medium containing results obtained using the method of any of claims 1-11.

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- 5 15. A storage medium containing results obtained using a method as substantially described herein.
  - 16. A system for determining gene network relationships, comprising:
    an input device for providing quantitative expression data for genes of an organism;
    a storage device adapted to receive quantitative expression data for genes of said organism;

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a processor adapted to carryout a Bayesian network analysis of network relationships between said genes, thereby producing a data set reflecting said network relationships; and an output device for displaying said data set of said network relationships.

17. A system for determining gene network relationships as substantially described herein.